REMARKS:

Applicants have amended the claims to expedite the prosecution of preferred embodiments. The Applicants reserve the right to prosecute any cancelled claims or subject matter in a continuation, divisional or continuation-in part applications, claiming priority to this application.

Applicants have amended the claims to a method of detecting target nucleic acids, where the nucleic acid binding portion of each complementation molecule is a ***nucleic acid or nucleic acid analogue*** probe. Accordingly, Claims 1 and Claim 21 have been amended based on original claim 13 to define *"wherein the first and second probe portions are nucleic acids or nucleic acid analogues"*. Claims 13 and 15 have been cancelled. Claims 1 and 21 have also been amended to clarify that the binding of the "nucleic acid probes" to the target nucleic acid to sites "located in close proximity" which is supported throughout the application, in particular in paragraphs [0017], [0022], [0031], [0039], [0059], [0061] to [0069], [0118], Example 2 and Figures 4 and 5 of the specification. Amendments to Claim 20 is supported by paragraphs [0025] to [0027], [0041], [0057], [0059], [0019], Example 2 and Figure 5 in the specification.

As such, Applicants respectfully submit that these amendments do not introduce new matter, and have obviated the rejections and their entry is respectfully requested.

Claim 1 was objected to for informalities.

The objection to Claim 1 because of the use of the term "selected to that" has been obviated by the amendment to claim 1 to clarify the nucleic acid probe portions of the complementation molecules bind to the target nucleic acids at "sites that are located in close proximity."

Claims 1-24 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. Applicants respectfully submit the amendments to Claims 1, 21 and the cancellation of Claim 13 and 15 have obviated this rejection.

Claims 1-3, 5-13, 15-17, 19 and 21-23 were rejected under 35 U.S.C. §102(e) for being anticipated by Michnick et al., (US 6,270,964).

Applicants respectfully disagree. However, to expedite prosecution, Applicants submit amendments to Claims 1 and 21 have obviated this rejection. At paragraph [0047] (on page 15) of the present specification, Applicants explain why the U.S. Patent Application 2003/0049688 (now Patent 6,929,916, which is a continuation of Patent 6,428,951, which is a continuation of the Michnick *et al.*, Patent 6,270,964 cited in

the office action) is different from the present invention because it does not teach the use of nucleic acids to bring together protein components of PCA. This is confirmed by reading Michnick *et al.* which states:

> "[PCA] can be adapted to detecting ***interactions of proteins*** with DNA, RNA or small molecules." ***(Emphasis added)***. [see column 29, lines 62-63].
>
> "The interaction must be triggered by a third entity, which can be any molecule that will simultaneously ***bind to the two proteins*** or induce an interaction between the two proteins causing a conformational change in one or both of the partners". ***(Emphasis added)*** [see Column 19 (line 66) to column 30 (lines 25].

The skilled artisan reading Michnick *et al.*, would agree with this. Michnick *et al.* clearly teaches that ***nucleic acid-binding proteins*** are required to bind to the nucleic acid. Michnick *et al.*, does not teach or provide any motivation to use alternative nucleic acid binding probes other than nucleic acid binding protein probes, stating "*an interaction* between the two proteins causing a conformation change". Further, Michnick *et al.*, teaches that a change in the nucleic acid binding ***protein probe*** confirmation is preferably part of the PCA.

Michnick *et al.*, also only teaches "known DNA or RNA [protein] ***binding motifs***" and "***RNA protein binding domains*** fused to one or the PCA fragments" (see column 31, lines 5-6 and lines 9-10). ***(Emphasis added)***. Applicants submit that one of the advantages of the present invention is the rapidity and ease of use of nucleic acid probes to direct complementation of the coupled polypeptide portions. Further, Applicants submit another advantage is ease of generating nucleic acid probes to bind to ***any*** target nucleic acid sequence. Furthermore, Applicants teach in paragraph [0091] of the specification that the present invention is particularly well suited for the development of ***sensitive*** and ***reliable*** detection of a target nucleic acids amongst other non-target nucleic acid sequences. For example, the present invention can used to detect target nucleic acid sequences with very minimal variances in the nucleic acid sequences, such as point mutations as compared to non-target nucleic acid sequences (see paragraph [0091]), as well use to identify target nucleic acid sequences of interest amongst a population of non-target nucleic acids (see paragraph [0093]).

Accordingly, Applicants respectfully submit that Michnick *et al.*, does not disclose use of a nucleic acid or nucleic acid analogue as a probe to bind the target nucleic acid which brings together the polypeptide portions of the complementation molecule. Accordingly, Applicants respectfully submit as amended claims 1 and 21 have obviated this rejection and rejections to claims 1-3, 5-13, 15-17, 19 and 21-23 should be withdrawn.

Claims 4 and 24 were rejected under 35 U.S.C. §103 for being obvious over Michnick et al., (US 6,270,964) in light of Sodroski et al., (US 5,654,192)

Applicants respectfully disagree for the reasons stated above and Applicants submit the amendments to Claims 1 and 21 has obviated this rejection. Applicants submit that even if, as the Examiner indicates, one would be motivated to substitute the enzymatic portion of the polypeptide fragments of Michnick *et al.* with a discontinuous epitope which could be detected by immunodetection using an antibody as taught by Sodriski *et al,* one would not come up with the present invention.

As discussed above, because Michnick *et al.*, only teach the use of nucleic-acid binding proteins to bind to the target nucleic acid for PCA of the enzyme polypeptide, a substitution of the enzyme polypeptide for an alternative detection protein would not teach the present invention. As explained above, Michnick *et al.*, teaches that it is the third entity that triggers the interaction between the two proteins. That is the exact opposite of this claim. The nucleic acid triggers the interaction of the two proteins. And it is only after such interaction that the antibody detects the already formed discontinuous epitope. Applicants submit that the present invention, as amended is directed to nucleic acids or nucleic acid analogues as probes to trigger polypeptide protein conjugation of a detection molecule such as an enzyme or discontinuous epitope. Accordingly, Applicants respectfully submit as amended claims 1 and 21 have obviated this rejection and rejections to claims 4 and 24 should be withdrawn.

Claim 18 was rejected under 35 U.S.C. §103 for being obvious over Michnick et al., (US 6,270,964) in light of Lizardi et al., (US 5,854,033).

Applicants respectfully disagree for the reasons stated above and Applicants submit the amendments to Claims 1 and 21 have further obviated this rejection. At paragraph [0120] of the present specification, Applicants explain why the present invention is substantially different from classic RCA because in the present invention, signal amplification is mostly gained by the enzymatic activity of the re-assembled protein as a result of probe mediated protein complementation of the polypeptide portions of the complementation molecule. Applicants submit that one of the advantages of the use of protein complementation to enable RCA in the present invention is that it results in *faster analysis* than in conventional RCA and is more *sensitive* as compared to hyper-branched RCA (see paragraph [0120] in the present specification).

Applicants submit that even if, as the Examiner indicates, one would be motivated to amplify the target nucleic acid of Michnick *et al.* using rolling circle amplification of Lizardi et al., one would not come up with the present invention, which in one embodiment, teaches nucleic acids or nucleic acid analogues as probes to bind to target nucleic acid which can be amplified by rolling circle amplification (RCA). Accordingly, Applicants respectfully submit as amended claims 1 and 21 have obviated this rejection and rejections to claim 18 should be withdrawn.

Claims 1 and 14 were rejected under 35 U.S.C. §103 for being obvious over Michnick et al., (US 6,270,964) in light of Landegren et al., (US 2002/0064779).

Applicants respectfully disagree for the reasons stated above and Applicants submit the amendments to Claims 1 and 21 have further obviated this rejection. Applicants point the Examiner to paragraph [0047] (on page 15, lines 14-19) of the present specification, which teaches that the present invention is different from Landegren et al., stating that:

> "Unlike in the present invention, in the Landergren approach, there is no protein complementation. Furthermore, the Landergren approach is essentially the ***opposite*** of the present invention, because the ***nucleic acids are brought into close proximity by the protein-protein*** interactions rather than the [present invention, where] proteins being brought into close proximity by the nucleic acid interactions". ***(Emphasis added)***

In particular, Landergren relates to use of proximity probes which comprise a binding moiety, such as a protein or nucleic acids, which binds an analyte, such as a protein or nucleic acid, and a reactive functionality.

> Landergren *et al.*, teaches in paragraph [0006] that the reactive functionality of the proximity probes interact "if two or more proximity probes .. [bind] to the individual analyte molecule"
>
> Landergren *et al.*, in paragraph [0011] teaches that "the reactive functionality of the proximate-probe is a nucleic acid bound to the binding moiety", and continues to say that the "As proximity probes are brought near each other, …. the ***coupled nucleic acids*** are ***also brought in vicinity of each other***. The proximity of these target bound nucleic acids is used to promote various detectable interactions between these nucleic acids. This nucleic acid interaction is detected in a secondary step of the analysis. In most cases, the secondary detection of the amount of nucleic acid interaction will involve a specific amplification of the interaction product".

Thus the skilled artisan reading Landergren *et al.*, is clearly taught that while the binding moieties which bind the analyte can be proteins or nucleic acids (see paragraph [010], the binding of at least two binding moieties to the target analyte ***brings together*** the ***nucleic acids*** reactive functionalities of the proximity probe, which is detected by a secondary analysis step. Thus, Landergren *et al.* does not teach, or make any suggestion to use nucleic acids as probes to bind to a third entity to direct a protein-protein interaction, or protein complementation. Nor does Landergren *et al.* suggest that the binding moieties can bring together alternative reactive functionalities other than nucleic acid reactive functionalities.

Accordingly, Applicants submit that even if, as the Examiner suggests, one would be motivated to use the complementary nucleic acid as the binding moieties of Landergren *et al.,* for protein complementation to form the complementation complex of Michnick *et al.*, one would still not come up with the present invention. While Landergren *et al.,* may teach protein-proteins interactions to result in nucleic acid interaction, it does not teach the use of nucleic acid interactions to result in protein-protein interactions or protein complementation. This differs in what can be detected and how you detect it. Accordingly, Applicants respectfully submit as amended claims 1 and 21 have obviated this rejection and rejections to claims 1 and 14 should be withdrawn.

Claim 20 was rejected under 35 U.S.C. §103 for being obvious over Landegren et al., (US 2002/0064779) in view of Michnick et al., (US 6,270,964) and Stefano et al., (US 6,287,772)

Applicants respectfully disagree for the reasons stated above and Applicants submit the amendments to Claims 1 and 21 have further obviated this rejection. While Stefano *et al.* teaches the use of two PNA probes to form a triplex with a target nucleic acid, it does not teach the use of two PNA probes to form a triplex with a target nucleic acid to result in protein-protein interactions or protein complementation. Applicants submit that even if, as the Examiner indicates, one would be motivated to substitute the triplex detection means of Stefano *et al* for the adjacent binding sites of Landegren *et al.,* as modified by Michnick *et al.*, one would not come up with the present invention, which in one embodiment, teaches nucleic acids or nucleic acid analogues as probes to bind to target nucleic acid to form a triplex to direct polypeptide protein complementation. The addition of Stefano *et al.,* Landegren *et al.,* and Michnick *et al.*, does not overcome the deficiencies discussed above. Accordingly, Applicants respectfully submit as amended claim 1 has obviated this rejection and the rejections of claim 20 should be withdrawn.

In conclusion, in view of the amendments to the claims and the arguments and evidence presented above, Applicants respectfully submit that all the claims are now in condition for allowance. Early and favorable consideration is solicited. The Examiner is encouraged to contact the undersigned attorney with questions regarding this amendment.

FEE AUTHORIZATION

Should any fee deficiencies be associated with this submission, the Commissioner is authorized to debit such deficiencies to Nixon Peabody Deposit Account No. 50-0850. Any overpayments should be credited to said Deposit Account.

Date: March 26, 2008

Respectfully submitted,

/Ronald I. Eisenstein/

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